IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Art Unit:	1634
Abreu, *et al.*	Examiner:	GOLDBERG, Jeanine
Serial No: 10/356,736		
Filed: January 30, 2003		
For: *MUTATIONS IN NOD2 ARE ASSOCIATED WITH FIBROSTENOSING DISEASE IN PATIENTS WITH CROHN'S DISEASE*		

DECLARATION OF KENT TAYLOR

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Kent Taylor, declare and state as follows:

1. I am the Laboratory Operations Director of the General Clinical Research Center's Phenotyping/Genotyping Laboratory at Cedars-Sinai Medical Center, Los Angeles, California. I am also a member of the Genetics of Common Diseases Group at Cedars-Sinai's Medical Genetics-Birth Defects Center, and an Assistant Professor of Pediatrics at the David Geffen School of Medicine at University of California, Los Angeles (UCLA). I provide genotyping data and bioinformatics support to the Genetics of Common Diseases Group and to various clinical investigators at Cedars-Sinai Medical Center. I

study the genetics of inflammatory bowel disease as a member of the Immunobiology Center, and teach in the Cedars-Sinai/UCLA Intercampus Genetics Program and in training programs for clinical investigators. I earned my doctorate in molecular biology from University of Southern California (USC) in Los Angeles.

2. I have personal knowledge of studies described and I am one of the inventors in the above-referenced patent application.
3. The present invention is based upon what I would view as highly significant data. Studies leading to the present invention were undertaken with great care so that results would be accurate and reliable. To achieve statistically significant data results, the study used a large population and ethnic determinations and disease diagnosis were made under stringent guidelines. These efforts included the use of two experimental cohorts rather than one, testing serum of ANCA and ASCA as serum immune markers associated with distinct clinical phenotypes of Crohn's disease, and the use of a panel of inflammatory bowel disease physicians unaware of the results of serologic and genetic testing that reached a consensus on phenotype based on the clinical data.
4. When examining a large number of variables, an appropriate correction is required for the number of tests performed. However, while common corrections such as Bonferroni correction result in a stringent statistical significance level for each individual variable examined, it reduces the power to identify specific associations between NOD2 and clinical variables because some of these traits are known to be associated with each other, such as small bowel involvement and ASCA expression. For this reason, the present invention is based upon a two-stage cohort strategy, made up of a hypothesis-generating cohort and a hypothesis-confirming cohort.
5. Studies reviewed in Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002), Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) and Meyer, et al. (U.S. Pat. Pub 2003/0092019) employed significantly different methodology than studies leading to the present invention. Factors that could cause irreproducibility of association studies such as population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, weak genetic effects, lack of power, bias, and population diversity, are not applicable to the present invention, due to the utilization of large population subjects, and stringent statistical and ethnic controls.

6. Similar to studies described in the abstract of Lakatos, et al. (Orv. Hetil. Vol. 145, No. 27, pages 1403-1411, July 2004), studies that formed the basis of the above-referenced application compared the frequency of NOD2 variants between experimental cohorts and control cohorts. However, the findings of Lakatos, et al. regarding G908R mutation associations are questionable. Without first establishing a link in a cohort between the G908R mutation and Crohn's Disease in general, that cohort cannot be relied upon for additional studies of the G908R mutation association with specific Crohn's Disease phenotypic expressions.
7. The conclusion of Ahmad, et al. (Gastroenterology, Vol. 122, pages 854-866, 2002) that the NOD2/CARD15 association with stenotic disease behavior is not independent from the ileal location is not reliable. Additional detail is needed beyond a statement that a logistic regression was performed to determine this conclusion.
8. A valid association study requires a population 3 to 4 times larger than the population used in a study it is trying to disprove. Neither Lakatos, et al., Vavassori, et al. (Inflamm. Bowel Dis., Vol. 10, No. 2, pages 116-121, March 2004), nor Ahmad, et al. utilized such a population, instead utilizing 142, 165 and 244 patients, respectively, compared with 201 patients in the present invention.
9. I am a co-author of the journal publication by Abreu, M., Taylor, K., Lin, Y., Hang, T., Gaiennie, J., Vasiliauskas, E., Kam, L., Rojany, M., Papadakis, K., Rotter, J., Targan, Yang, H.; "Mutations in NOD2 are Associated with Fibrostenosing Disease in Patients with Crohn's Disease;" *Gastroenterology,* Volume 122, No. 4, Supplement, page A-29, 246 ("the Abreu, et al. Vol. 122 Reference"). Drs. Lin, Hang, Gaiennie, Vasiliauskas, Kam, Rojany, and Papadakis are co-authors of the Abreu, et al. Vol. 122 Reference, but are not co-inventors of the subject matter of the above-referenced application.
10. The work described in the Abreu, et al. Vol. 122 Reference is the joint work of Drs. Abreu, Rotter, Yang, Targan, and I. To the extent that any subject matter disclosed in the Abreu, et al. Vol. 122 Reference is described and/or claimed in the above-referenced patent application, the work relates only to the inventive contribution of myself and Drs. Abreu, Rotter, Yang, and Targan and not to the contributions of our co-inventors.
11. I am a co-author of the journal publication by Abreu, M., Taylor, K., Lin, Y., Hang, T., Gaiennie, J., Landers, C., Vasiliauskas, E., Kam, L., Rojany, M., Papadakis, K., Rotter,

J., Targan, Yang, H.; "Mutations in NOD2 are Associated with Fibrostenosing Disease in Patients with Crohn's Disease;" *Gastroenterology,* Volume 123, pages 679-688, August 29, 2002 ("the Abreu, et al. Vol. 123 Reference"). Drs. Lin, Hang, Gaiennie, Landers, Vasiliauskas, Kam, Rojany, and Papadakis are co-authors of the Abreu, et al. Vol. 123 Reference, but are not co-inventors of the subject matter of the above-referenced application.

12. The work described in the Abreu, et al. Vol. 123 Reference is the joint work of Drs. Abreu, Rotter, Yang, Targan, and I. To the extent that any subject matter disclosed in the Abreu, et al. Vol. 123 Reference is described and/or claimed in the above-referenced patent application, the work relates only to the inventive contribution of myself and Drs. Abreu, Rotter, Yang, and Targan and not to the contributions of our co-inventors.
13. I declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application and any patent issued thereon.

Kent Taylor, Ph. D.

20Sep2007
Date